Combined Injury in Radiation Threat Environments and Countermeasure Evaluations

G. David Ledney, Ph.D.

Armed Forces Radiobiology Research Institute,
Uniformed Services University of the Health Sciences

Bethesda, MD 20889-5603

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Contributing Investigators

- Itzhak Brook, M.D.
- Thomas B. Elliott, Ph.D.
- Michael O. Shoemaker, Ph.D.
- Gregory B. Knudson, Ph.D.
- Gary S. Madonna, Ph.D.
- W.E. Jackson, III, M.S.
- David L. Bolduc, M.S.
- Dianet E. Giraldo, M.S.
- Rita A. Harding, M.S.
- M.M. Moore, M.S.
- E.D. Exum, M.S.

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Combined Injury (CI) Defined

- "Injury that occurs only after exposure of the irradiated tissue to still another trauma, with a subsequent definite change in the tissue– an injury produced that is no way related to the low level of the second exposure." H. Wintz, 1923.
- "Injuries combined with radiation injures, especially nuclear weapon injuries." O. Messerschmidt, 1974.
- Illness, disease, or injury sustained from exposure to a radiation dispersal device (RDD) or nuclear weapon combined with the intentional use of microbial pathogens or chemical agents.

RDD

Nuclear

Experimental Background

- Standardized for High Throughput in Radiation Facilities and to Control Variability
- Animals-B6CBF1♀, B6D2F1♀, C3HeN♀ Mice:
  12-20 wks of age, 22-30 gr body mass
- Radiation Sources and Quality
  - Whole Body Doses Delivered at 0.4 Gy/min MLT
  - ^{60}Co γ-Photon : RDD
  - Mixed-Field Neutrons/ γ-Photon : Nuclear Weapon
- Injuries
  - 15% Total Body Surface on Shaved Anterior Dorsum
    - Wounds: via clean stainless steel punch on Teflon Board
    - Burns: via 12 sec ignition of alcohol

Mouse Model for Combined Injury Studies

γ-photon Radiation or
Neutron Radiation
0.4 Gy/min

15 % Dorsal
Skin-wound or
Skin-burn

0 hr → +1 hr → 30-day survival

B6D2F1, B6CBF1,C3H/HeN
female mice, 12-20 wks

Characteristics and Responses of ^{60}CO-γ-Photon Irradiated Mice to Skin Injuries

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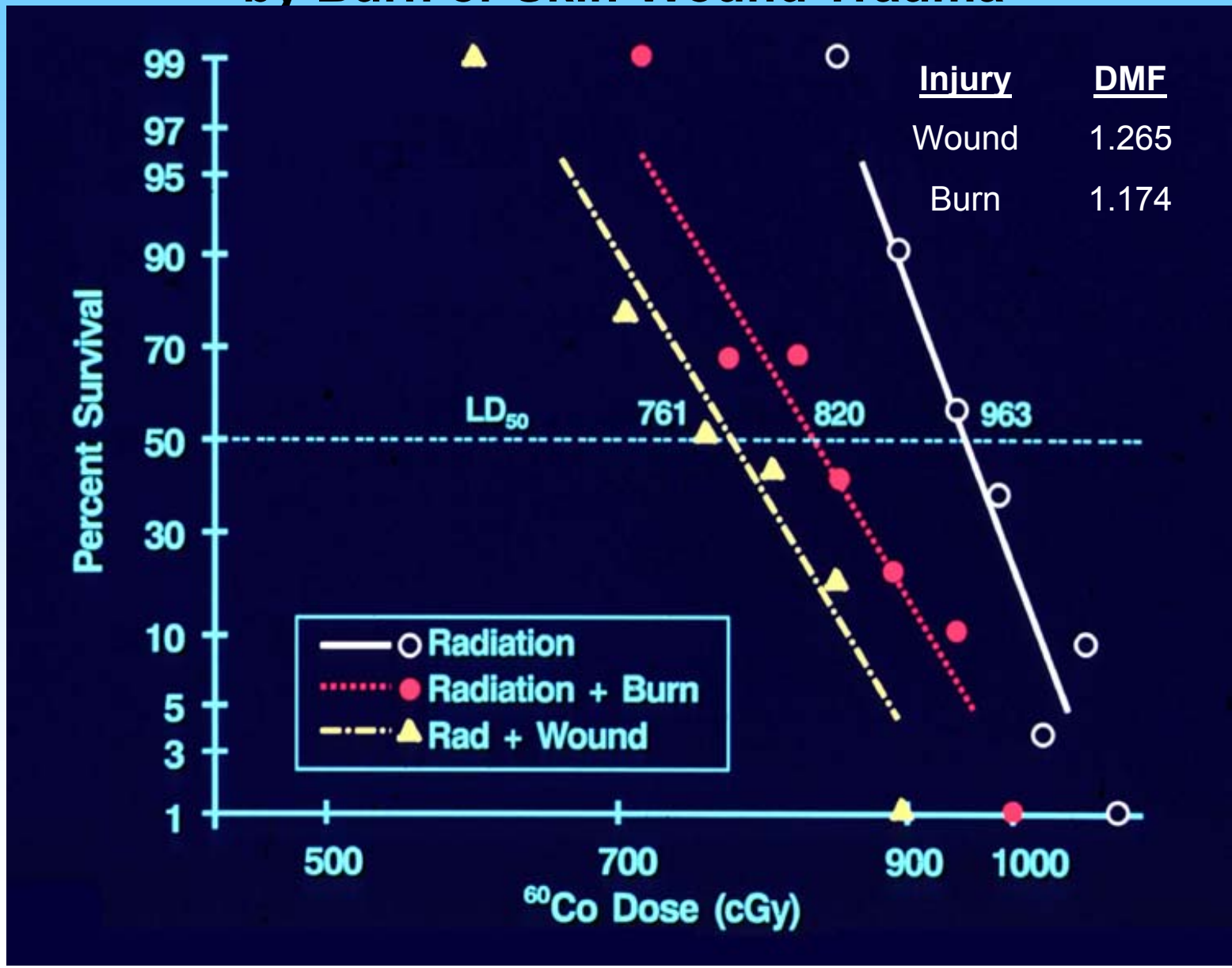
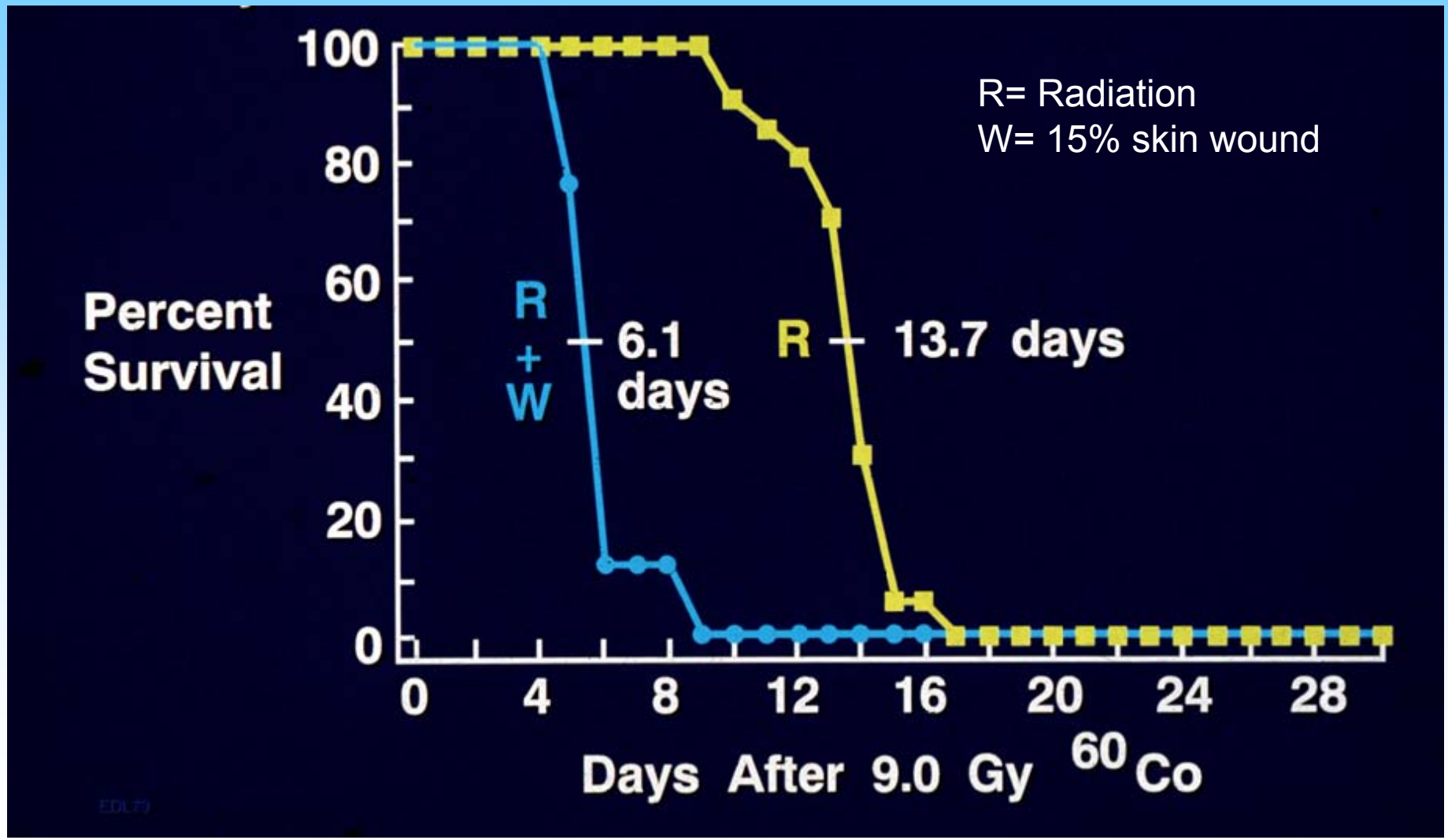
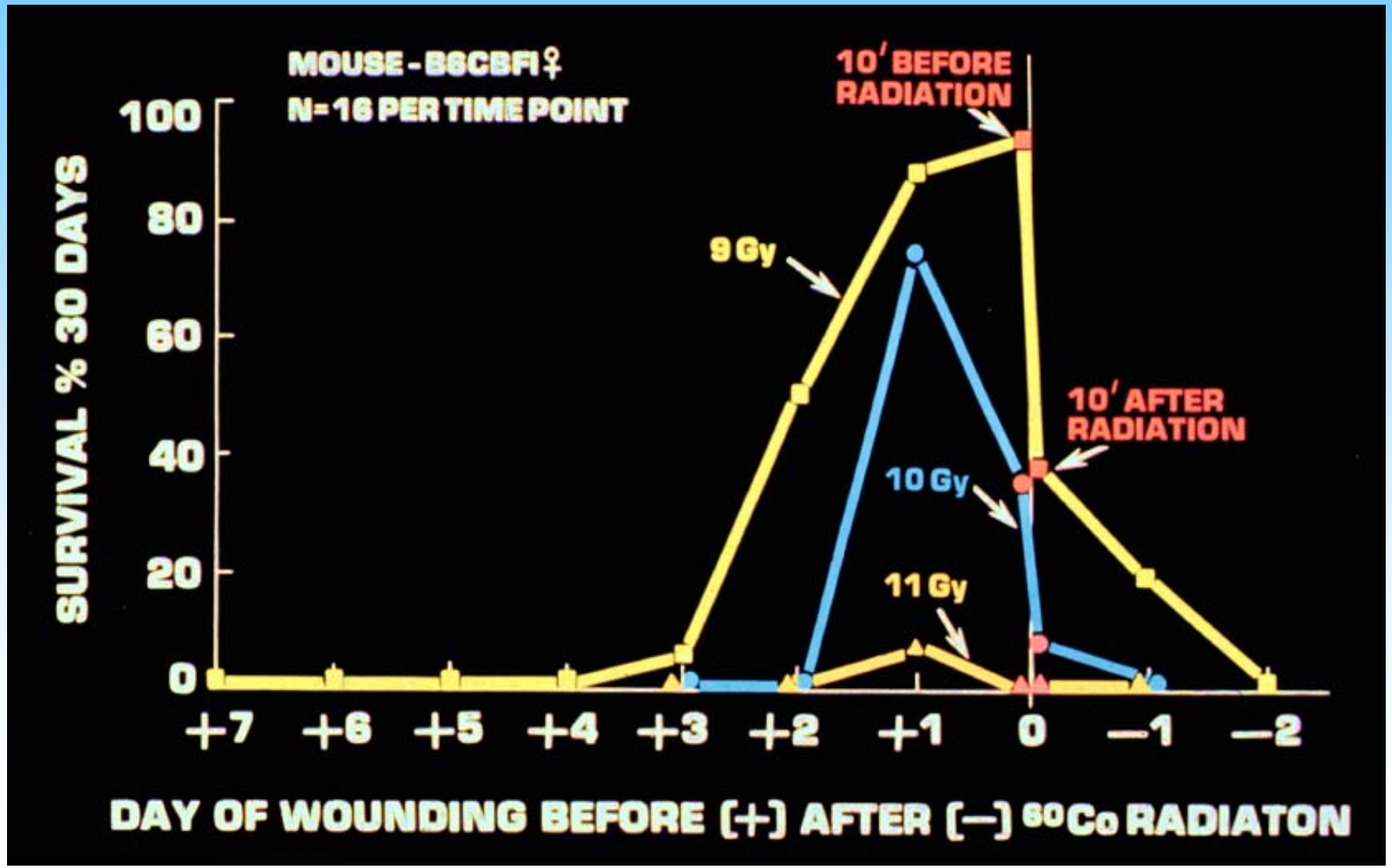
$LD_{50/30}$ for Gamma Radiation Decreased by Burn or Skin-Wound Trauma



Survival Time Decreased by Wounding After Lethal Irradiation



Survival After CI Depends on Timing of Wounding Relative to Radiation Dose



Characteristics and Responses of TRIGA-Reactor-Irradiated Mice to Skin Injuries

Rationale: Radiation exposures will be mixed-fields in real scenarios

AFRRI facilities uniquely designed for

- ❑ Animal irradiation
- ❑ Production of mixed neutron & γ-photon radiation fields
  - Mixed-field n/(n+γ) = 0.67
  - Enriched-Field n/(n+γ) = 0.95

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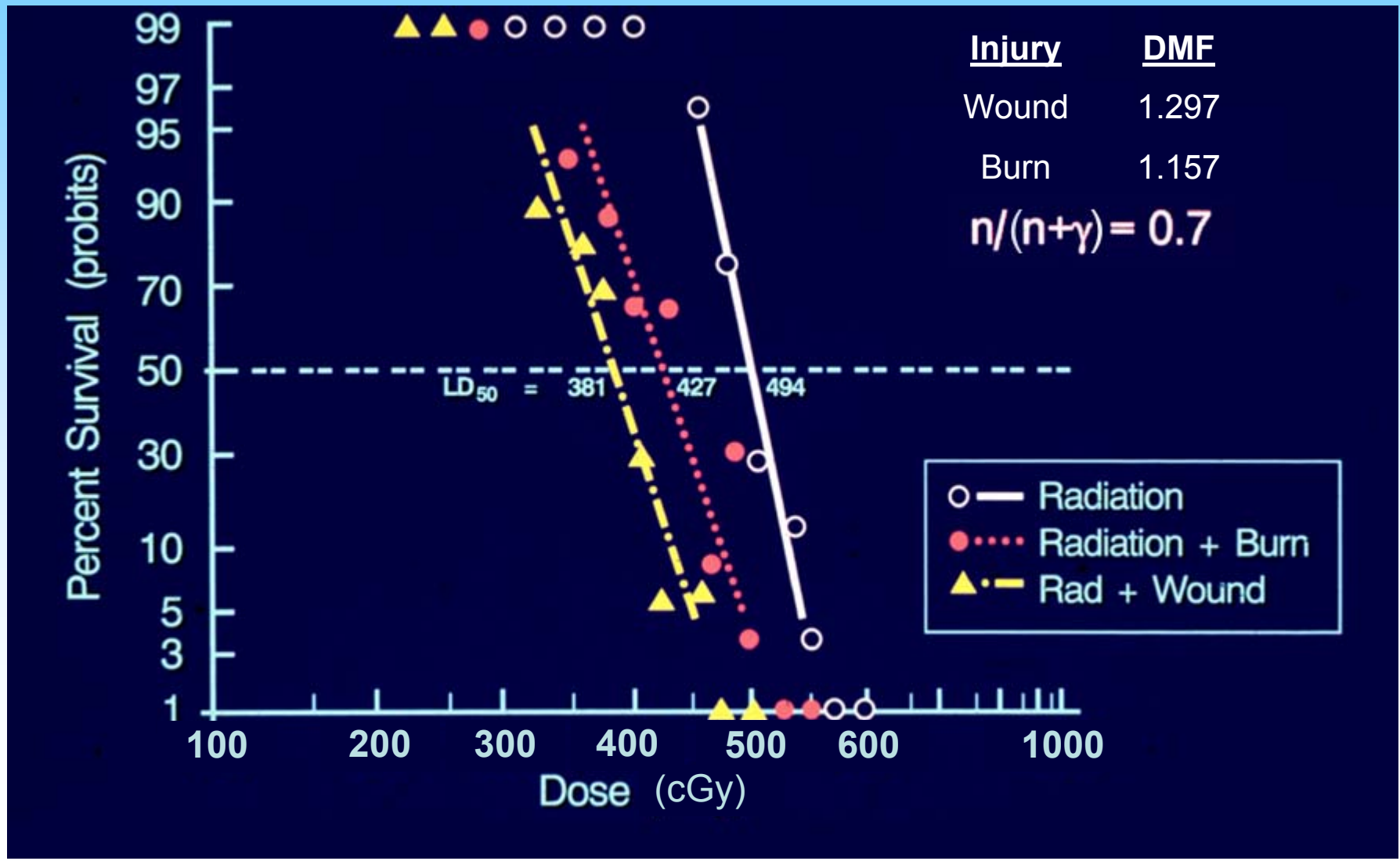
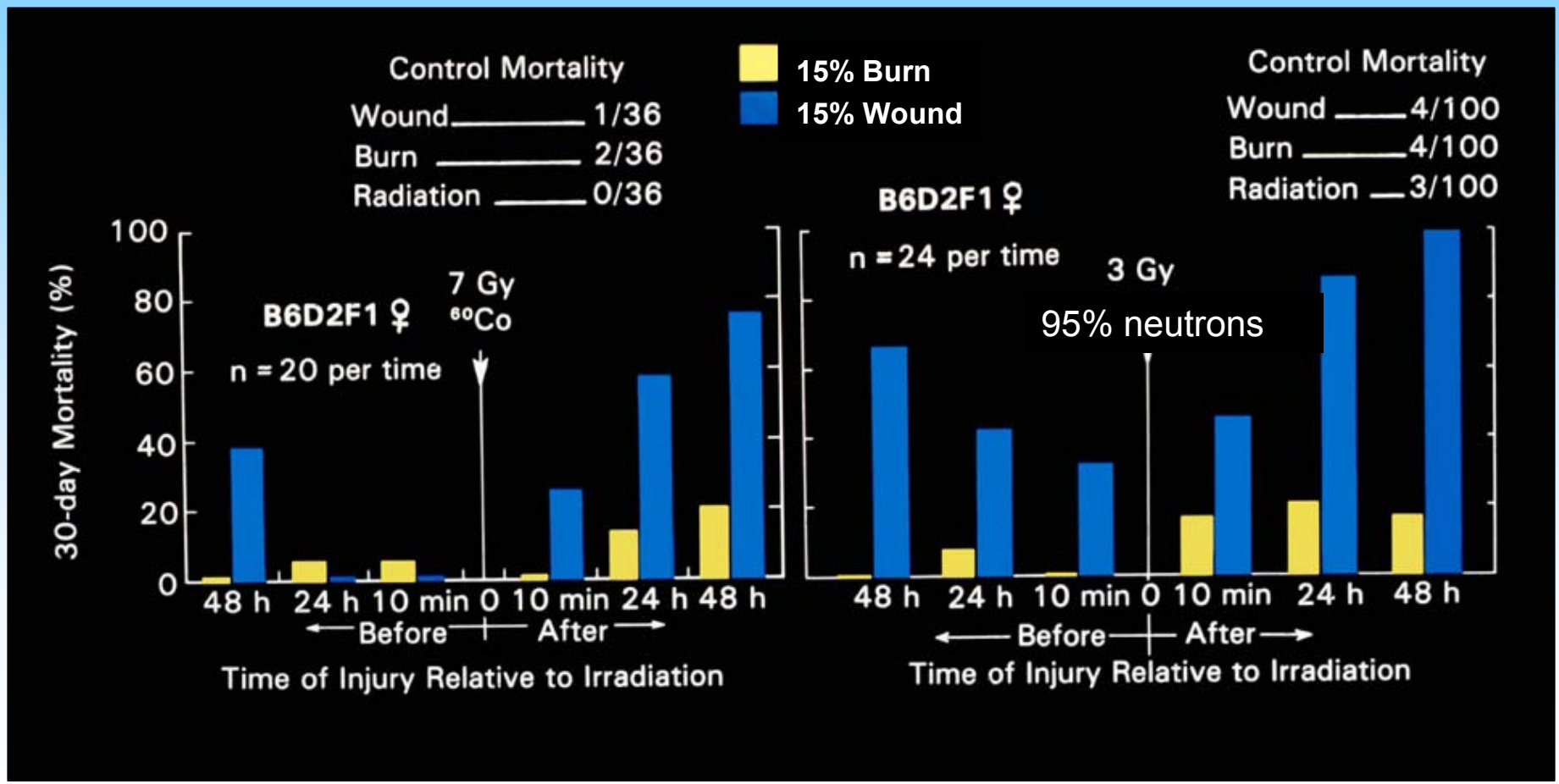
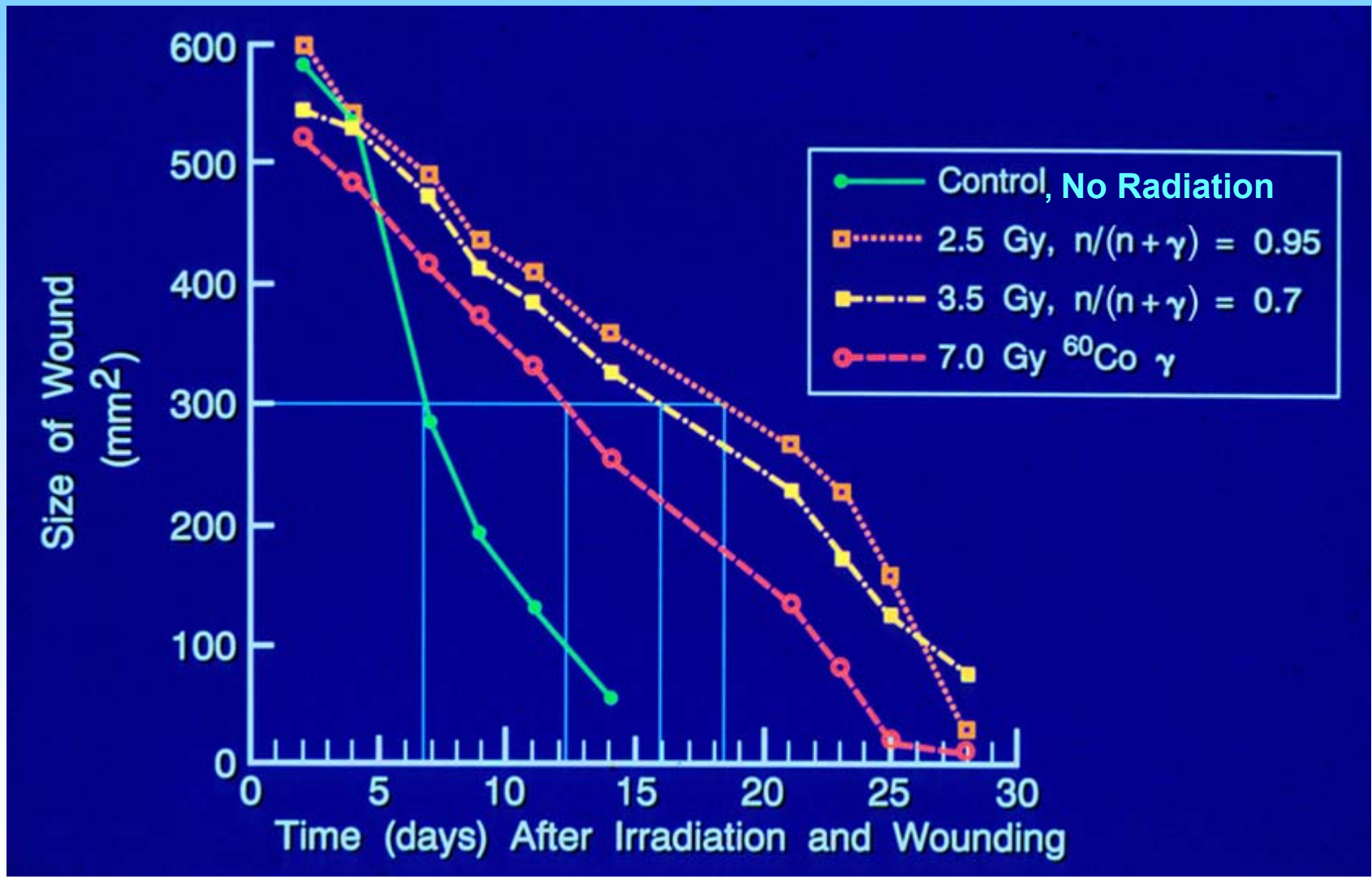
$LD_{50/30}$ for Mixed-Field Radiation Decreased by Burn or Skin-Wound Trauma



Mortality After CI Depends on Injury Type, Timing of Injury, and Radiation Quality



Wound Closure Time is Increased In CI Mice



Countermeasure Evaluations for Sequelae of Combined Injury

WR-151327
Antibiotics
Immunomodulators
Bone Marrow Transplantation

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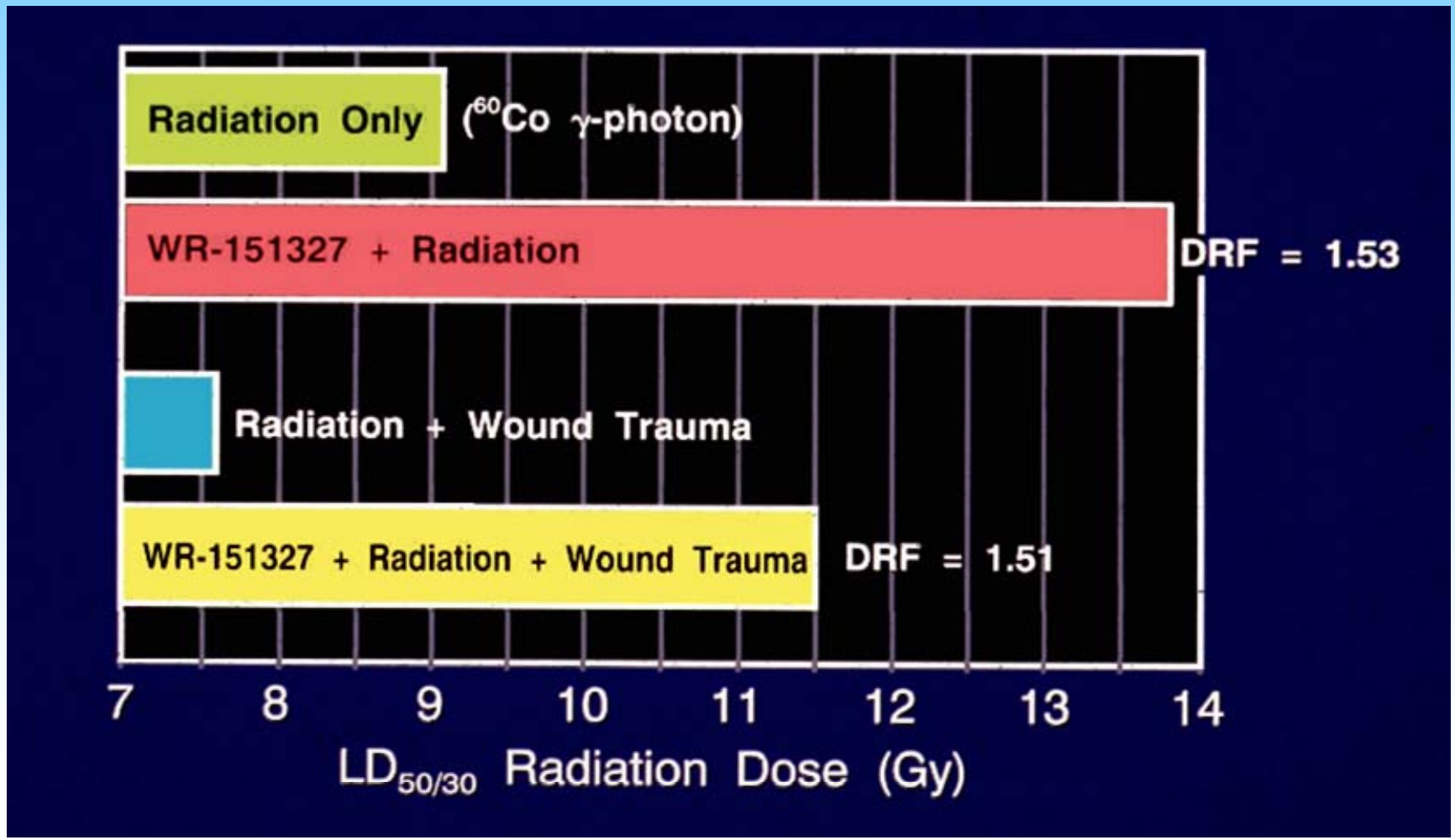
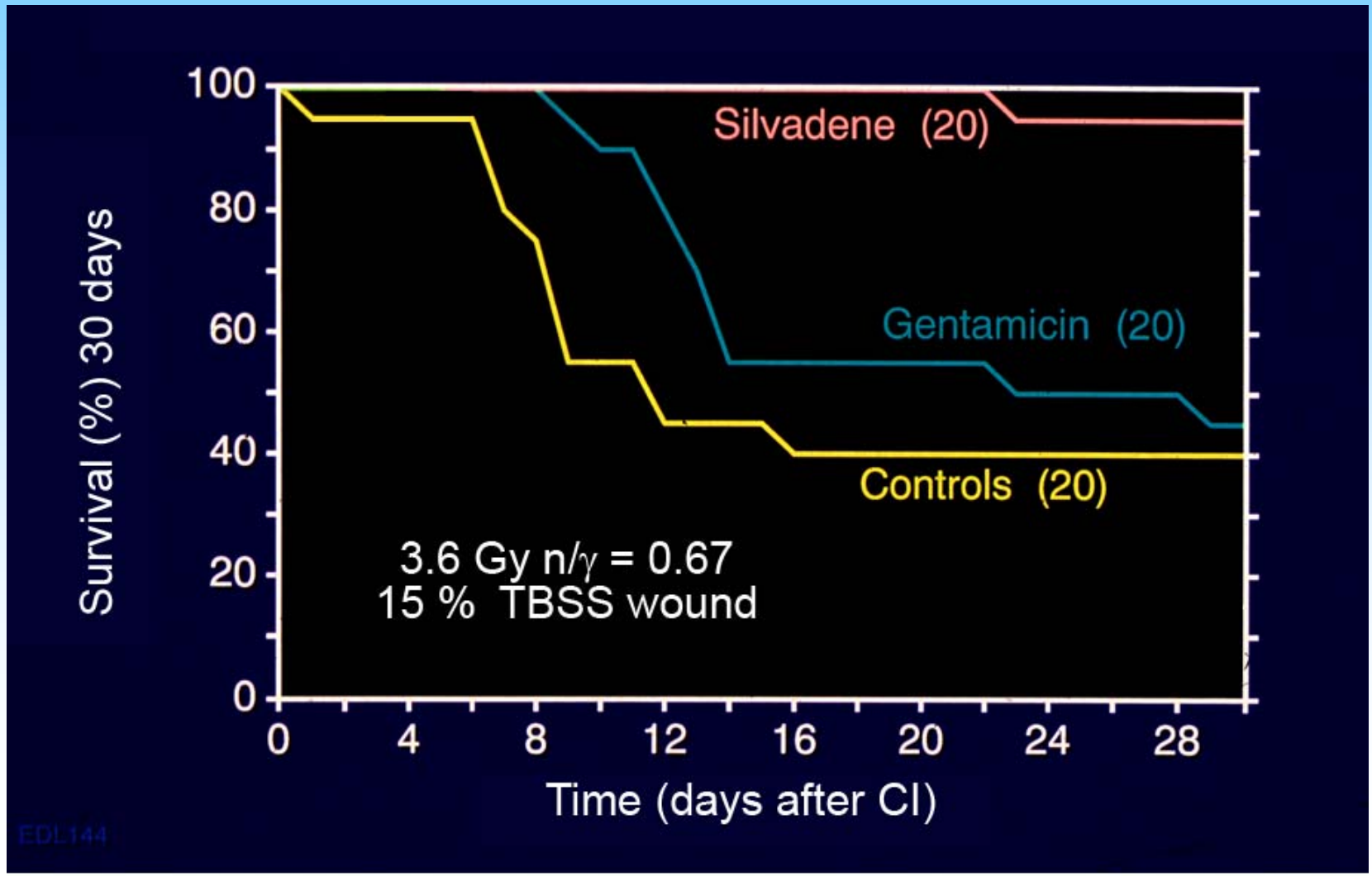
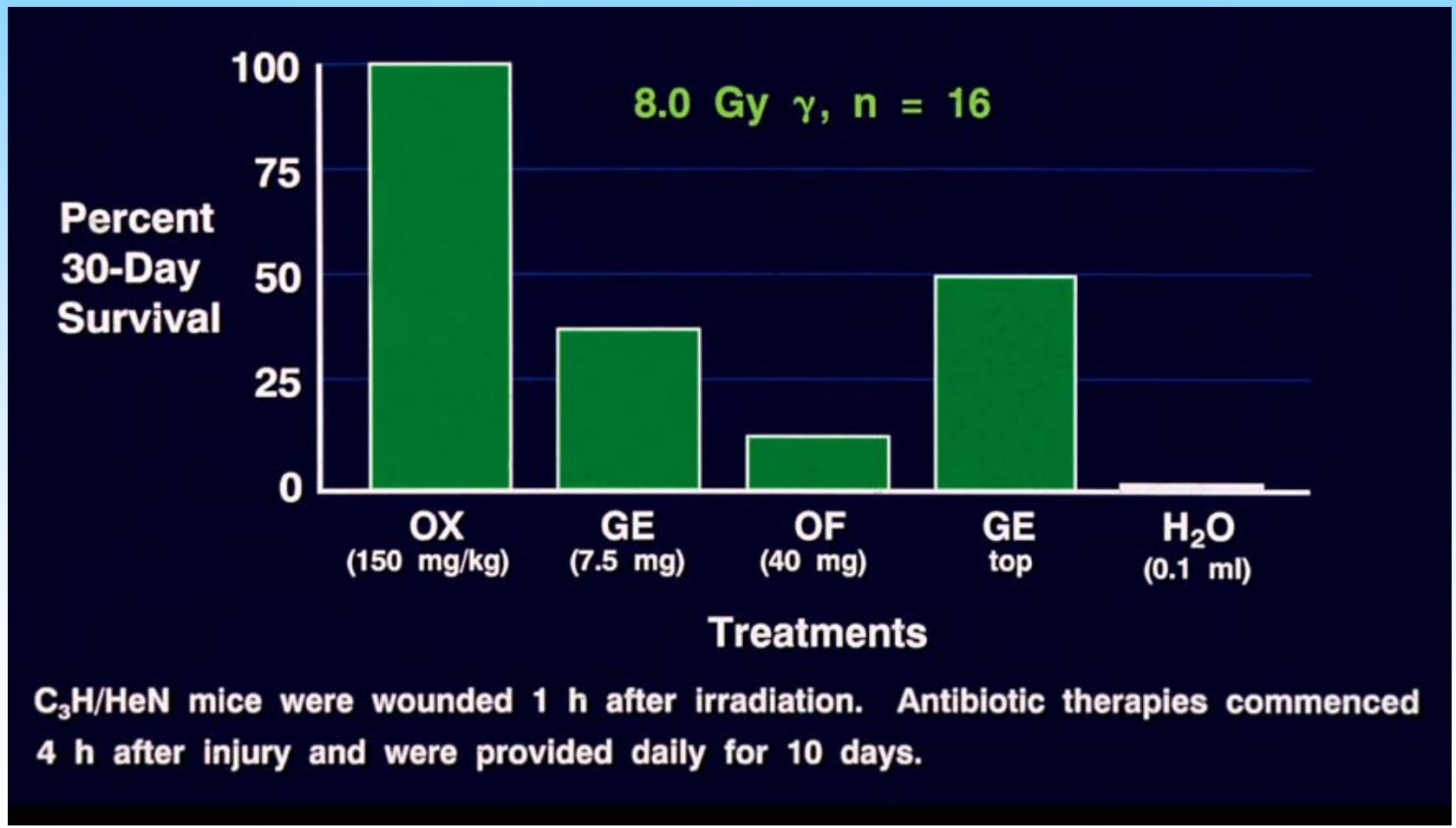
WR-151327 Provides A Similar Measure Of Protection [Similar DRFs] In ^{60}Co γ-Photon Irradiated and In Combined Injured Mice.



Survival of C3H/HeN Mice is Increased with Topical Silvadene Cream after CI

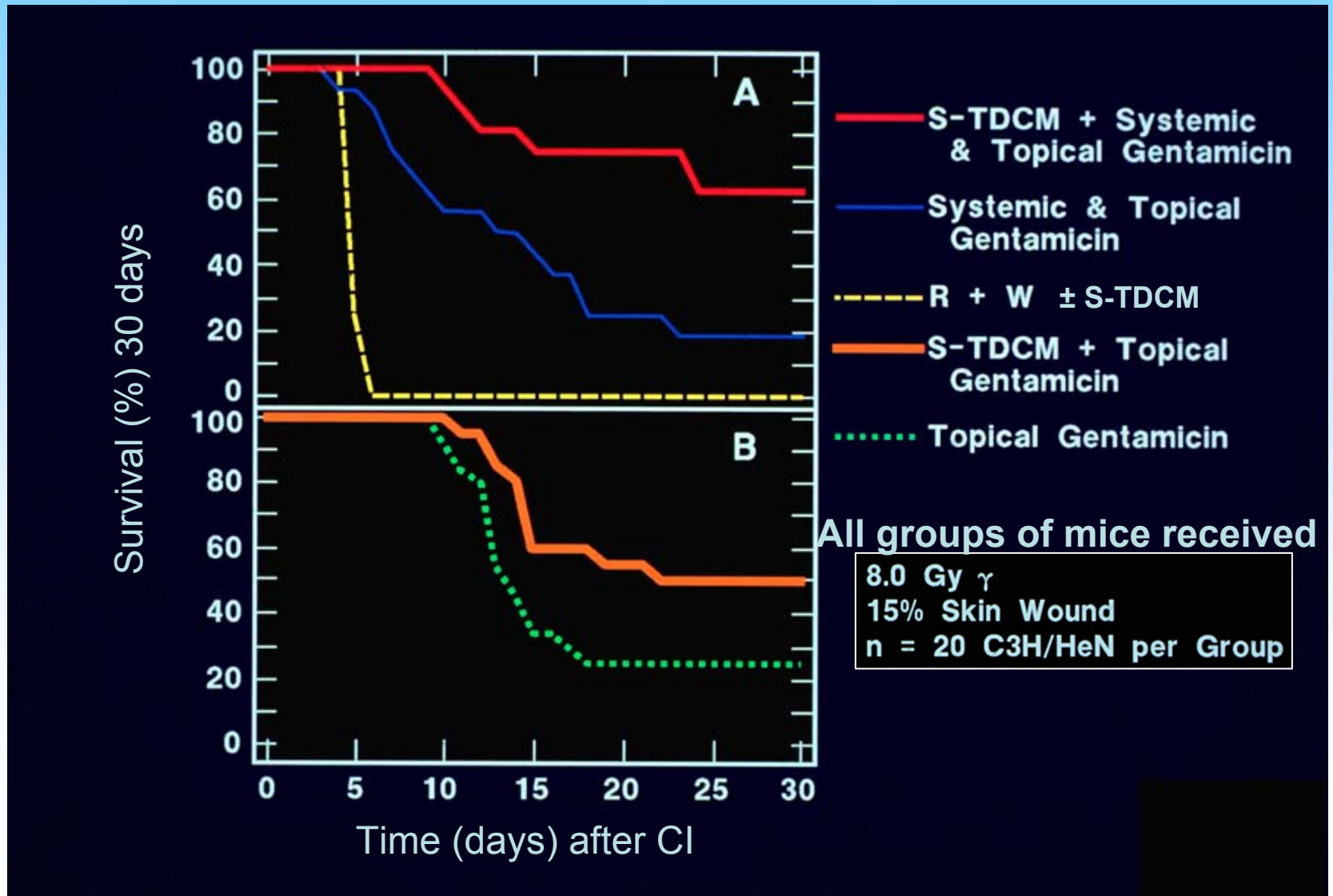


Topical Gentamicin Sulfate (0.1%) and Systemic Antibiotics Increase Survival from CI

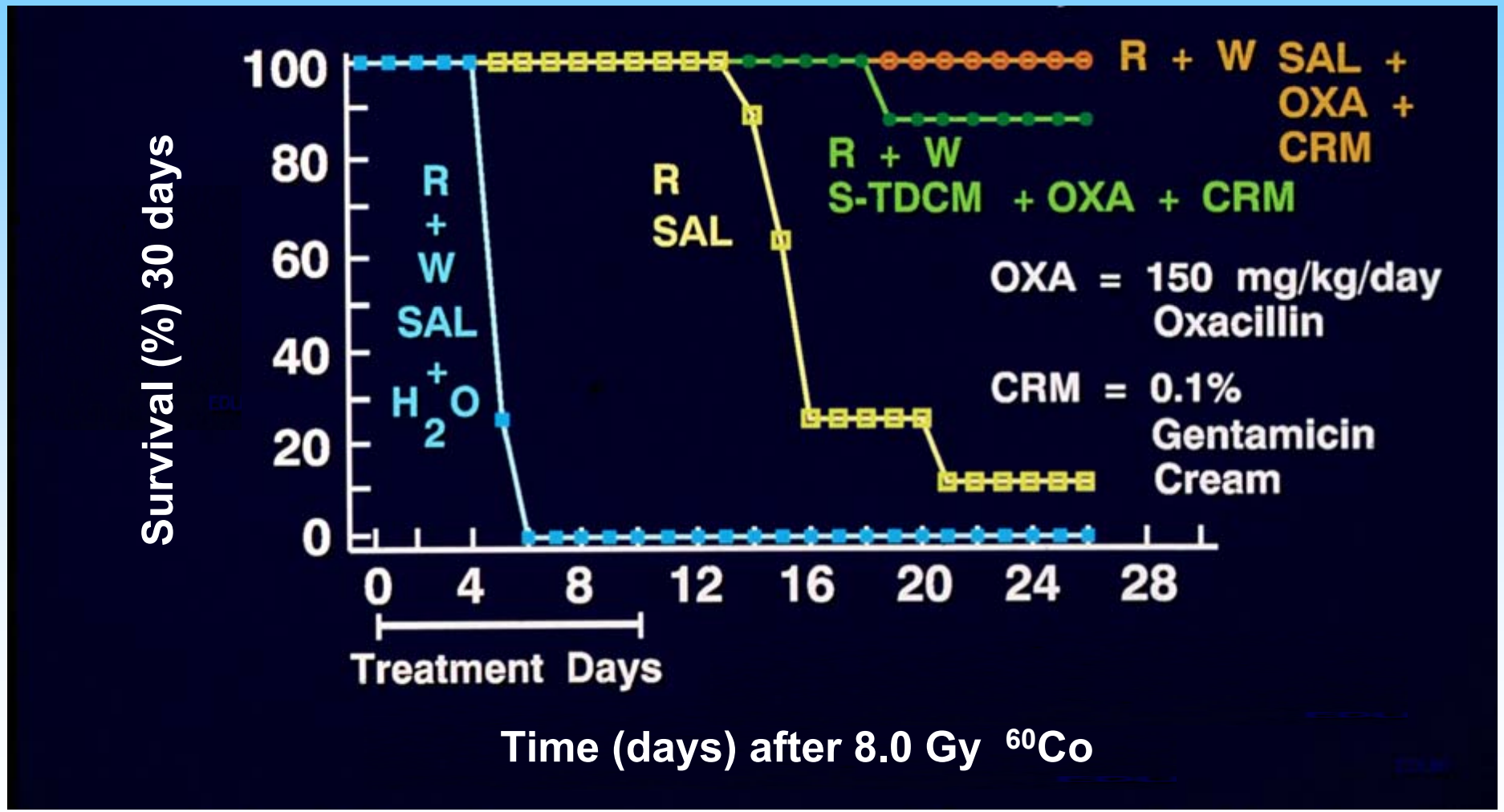


C_3H/HeN mice were wounded 1 h after irradiation. Antibiotic therapies commenced 4 h after injury and were provided daily for 10 days.

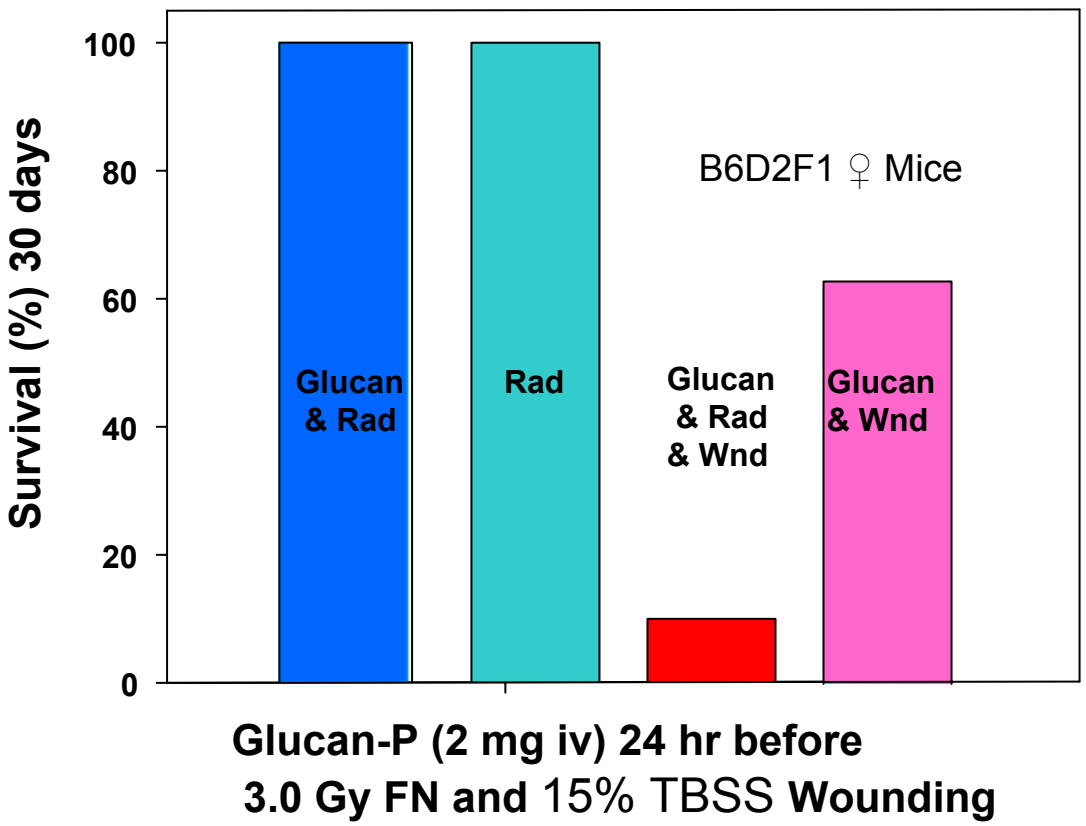
S-TDCM with Gentamicin Increases Survival from CI



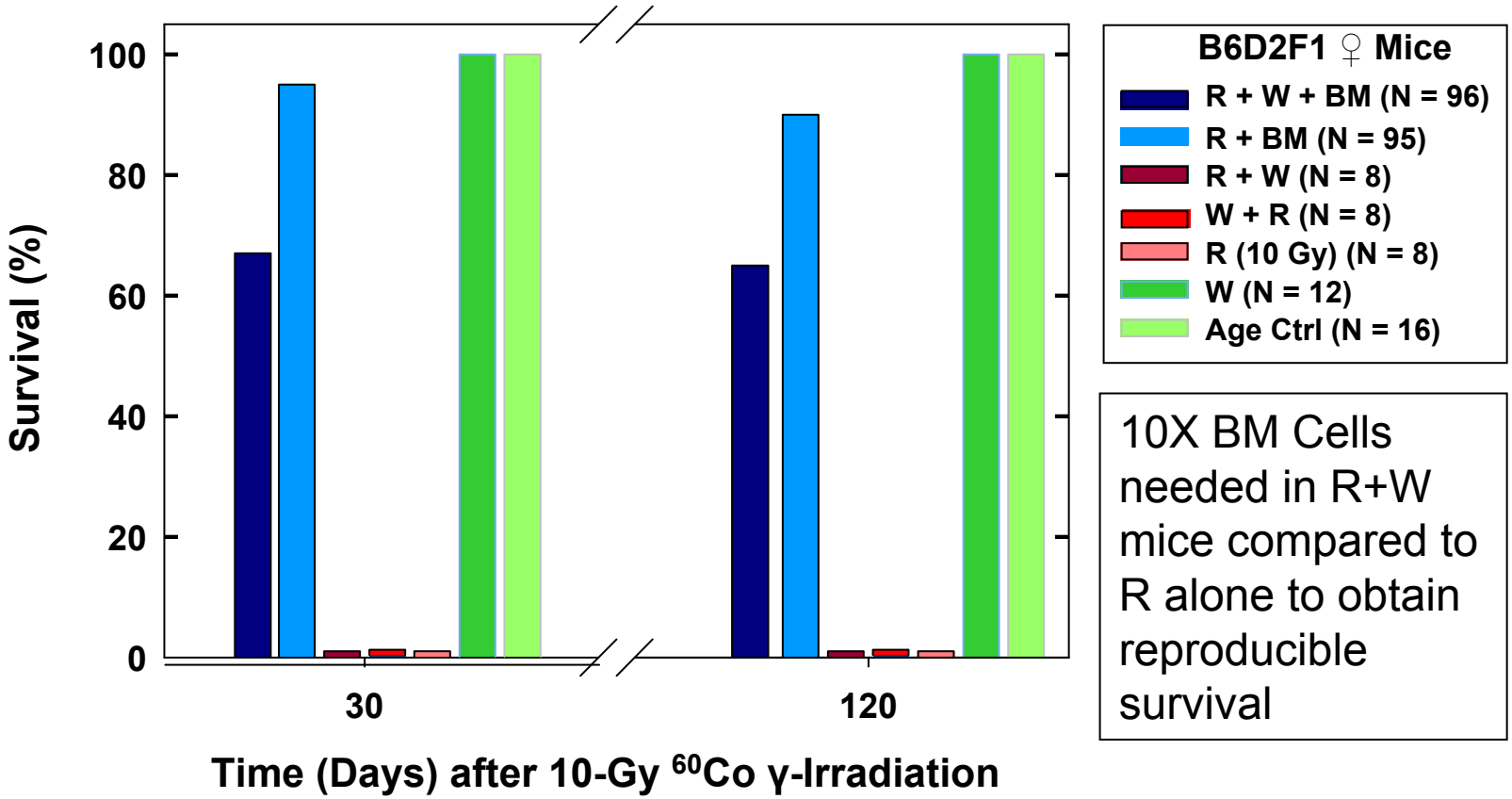
Antibiotics or Antibiotics with S-TDCM Enhance Survival of Combined Injured Mice



Glucan-P: Ineffective as A Countermeasure for Combined Injury



Syngeneic Bone Marrow Transplantation Rescues Mice from Combined Injury



10X BM Cells needed in R+W mice compared to R alone to obtain reproducible survival

Summary

Combined Injury in Radiation Threat Environments and Countermeasure Evaluations

- Skin traumas increase mortality from radiation
- Survival depends on type and timing of injury and radiation quality
- Dose Modifying Factors (DMF) after mixed-field and γ-photon irradiation and skin traumas are similar
- WR-151327 increases survival from CI
- Topical, systemic antimicrobials with S-TDCM increased survival from CI
- Glucan-p may be contraindicated as therapy for CI
- Bone marrow transplantation improves survival from CI

Future Directions

- Larger animal species and other injuries: *Sus scrofa domestica*?
- Mechanism of how & why tissue injury, after irradiation, increases lethality.
- New therapeutic approaches needed! Mechanism of action of immunomodulatory agents determined?
- Development and efficacy testing of newer antimicrobials: Anti-fungals! Fluoroquinolones!